

Protocol Title: Navigation of the Pelvic Floor in Bladder Exstrophy using Pre-operative MRI

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Investigational Device(s): VectorVision® Cranial Guided Image System  
Brainlab, Inc.

IDE Number: *Pending*

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## **1. Abstract**

Classic bladder exstrophy is a complex birth defect that involves malformations of the genitourinary and musculoskeletal systems. This defect occurs in approximately 1:30,000 to 50,000 live births, and occurs more often in males than females [1]. The abdominal wall musculature fails to mature properly in the midline of the body leaving the bladder literally splayed open on the anterior surface of the neonate. Additionally, the urethra is completely open (epispadias) and the entire penis has failed to roll into a tube. The pubic bones are widened and have also failed to fuse properly in the midline. This birth defect, while extensive, is surgically correctable with a multi-stage operative plan over the child's formative years. Initially within a few days of life, the bladder and abdominal wall undergo closure. This is often accomplished with the use of pelvic osteotomies, which leave the child with external fixation devices postoperatively. The fixator devices are removed after 4-6 weeks of pelvic immobilization. The second stage involves early repair of the epispadiac penis. If the bladder grows to a sufficient volume, then the child undergoes a continence procedure around age 5 that allows for volitional voiding. Some children's bladders grow appropriately and others fail to grow appropriately. If the bladder does not sufficiently grow, then additional and considerably more complex continence procedure and bladder augmentation are required to make the child continent[2].

Much of the long-term success of these operations depends on the initial closure. Several studies have demonstrated that a key to successful initial closure involves deep dissection of the pelvic floor so that the bladder can be placed in the most posterior and inferior position possible [3-5]. Oftentimes, the need for repeat closure of the abdomen is required if the initial surgeon failed to properly dissect deep enough into the child's pelvic floor. Many surgeons are unfamiliar with the complex anatomy and are unable to verify that they have properly reached the true pelvic floor during this initial surgery. This often leads to failed closures, which result in poor continence rates later in life [2].

It is our hypothesis that the use of intraoperative stereotactic imaging will help verify where the surgeon is during his or her dissection during closure of bladder exstrophy. We anticipate that successful use of stereotactic imaging will help improve the success rate of initial closure and long-term continence rates.

The value of this research is two-fold. Firstly, the project will help us to verify if we are indeed dissecting down to the proper plane required for successful initial closure of bladder exstrophy. Secondly, this project will help others with relatively less experience with bladder exstrophy to properly identify where they are anatomically during closure of exstrophy, thus yielding higher success rates and better patient care.

## **2. Objectives**

### **2.1. The primary objectives of this research are:**

- a. To determine the safety and efficacy of the use the Brainlab, Inc. VisionVector® Cranial Image Guided Surgery System during closure of bladder exstrophy.
- b. To verify the proper plane of dissection during closure of bladder exstrophy using the VisionVector® Cranial Image Guided Surgery System by visualizing in real-time where the surgeon's instruments are relative to the levator muscles and confirming that the bladder is being placed in the most posterior and inferior location possible.

## **2.2. The secondary objectives of this trial are:**

- a. To improve the overall success rate of closure of bladder exstrophy as evidenced by lower rates of postoperative prolapse, dehiscence, and fistula formation as well as improved continence when compared with the current standard of care, which does not currently involve the use of image guided surgery.
- b. To decrease the learning curve for pediatric urology surgeons associated with closure surgery [6].

## **3. Background**

Other surgical fields, such as neurosurgery and otolaryngology, have successfully utilized stereotactic imaging technology to improve accuracy and success of surgical dissection and oncologic control through various procedures. This technology has resulted in less-invasive procedures with greater technical ease and confidence that the surgeon is truly in the correct anatomical location. The VectorVision Cranial Image Guided Surgery System (by Brainlab, Inc.) is an FDA-cleared device indicated for use in neurosurgery and otolaryngology as shown on the attached 510K summary. Several studies have been published demonstrating the safety and success of this device in stereotactic surgery [7].

The Cranial IGS system consists of the IGS workstation, the touch screen monitor and the optical 3D tracking system. It also includes a set of hardware accessories that provide for comfortable and accurate use of the system. The IGS workstation holds the patient data during the surgical procedure and runs the cranial software application. The patient data needed in order to perform the image guided surgery is acquired pre-operatively and is transferred to the IGS workstation via network, data carrier, or data bus.

The iPlan Cranial® allows for pre- and intraoperative stereotactic surgery planning based on stereotactic systems. Multiple graphical display functions and 3-dimensional views of anatomical structures offer effective and efficient means of presenting the anatomical data for diagnostic and surgical planning. Software application offers a display of the patient data in various reconstructions, segments and overlays on the touch screen monitor in addition to position information of tracked instruments. The touch screen monitor allows the control of the iPlan Cranial® software application and can be draped for sterile use by the surgeon. The optical 3D tracking system performs the localization of the patient and surgical tools within the operating field.

The virtual diagnostic image spaces are registered to the surgical environment by collecting the 3D position of anatomical landmarks with a tracked pointer probe and relating them with the corresponding features extracted from the diagnostic image data sets.

Intra-operatively acquired patient data can further be registered to the surgical environment by determining its spatial position in relation to the patient during its acquisition. Structures in the patient's body are localized using trackable pre-calibrated or intra-operatively calibrated surgical instruments such as the pointer probe. In addition to the pointer probe, various standard surgical equipment such as forceps and scissors can be calibrated and used for spatial positioning.

The Cranial IGS System contains a network based software interface that allows downloading medical data (such as image sets, objects, trajectories, or points) and tracking data from the system as well as uploading and displaying an image stream to the system. This interface can be used to implement custom visualization of medical data (e.g. included modalities which are otherwise unknown to the cranial software application) as well as to control other devices. These view data is strictly under the responsibility of the user and clearly marked as such.

Per the 510(k) clearances, these devices are currently indicated for adults and children with any medical condition where stereotactic surgery may be appropriate and where a reference to a rigid anatomical structure, such as a bone, can be identified relative to MRI or other similar imaging modality. The device has multiple utilities across various surgical fields and is routinely used in neurosurgery, spine surgery, and otolaryngology.

Studies from various institutions have demonstrated that successful outcomes in bladder exstrophy surgery rely upon proper anatomical dissection during surgery. Studies involving pre- and post-operative MRI have demonstrated this [8]. Furthermore, it has been well established that many bladder exstrophy closures fail because the bladder was not placed deep enough into the pelvis [5]. This is thought to be secondary to the surgeon's unfamiliarity with the patient's anatomy in this rare congenital anomaly, thus leading to placement of the bladder in a superficial plane, predisposing the patient to potential failed closure [9].

We propose to use this intraoperative stereotactic imaging system as a guide during the pelvic dissection in children ages 0-7 years that require closure of bladder exstrophy as we hypothesize that it will aid in identification and verification of the proper plane required for successful initial closure. Due to the nature of bladder exstrophy, this study cannot be done on adults. However, according to multiple studies, image guided surgery can be as safe and beneficial in the pediatric population as it has shown to be in adults [10-11]. We expect that, as seen with applications in other various fields, the use of image-guided surgery will allow for improved visualization and accurate navigation of the planned surgery [10, 12-13]. Additionally, the use of image-guided surgery should allow the possibility of extending the pelvic dissection safely in order to place the bladder in closer proximity to the puborectalis and levator ani muscles, allowing these muscles to aid in increasing bladder capacity postoperatively and ultimately increasing the rate of successful exstrophy closure and urinary continence [14]. We also expect that the use of image-guided surgery will result in a similar reduction in morbidity and mortality as well as a shortening of hospital stay.

#### **4. Study Procedures**

##### **4.1. Study design**

This is a prospective, single arm, interventional trial of 60 subjects aged 0-7 years who require bladder exstrophy closure as part of routine medical care.

##### **a. Minimizing Bias**

Blinding is not applicable to this study design. The surgery and management of this procedure will be carried out exactly as in standard clinical practice with the exception of adding confirmatory intra-operative stereotactic imaging. As such, a placebo group or non-treatment group is not applicable to this study.

##### **b. Treatment Failure/Patient Removal**

This study does not involve any change to specific disease treatment, so treatment failure definition is not appropriate for this trial. A patient may be removed from the study based on the wishes of their parent/guardian or if a member of the designated group of faculty in charge of safety monitoring (outlined in section 11) feels that the safety of the patient is jeopardized by the new intervention. Studies show that as high as 63% of closures fail [15]. The designated faculty will work to determine if the treatment failures are a result of this designated intervention and if so patients will be withdrawn. Any data collected up to the date of patient/guardian withdrawal of consent will be kept and included in study analyses. Any patients removed from study will be replaced.

#### **4.2. Study Duration**

The study is anticipated to take two years in order to enroll and evaluate short-term outcomes for a maximum of 60 patients. Each patient will be considered “on-study” from date of informed consent through and including the day of their planned surgery. Study “follow-up” will begin the first post-operative day and end 12 months later. The study will require no additional visits or procedures beyond the standard clinical practice for bladder exstrophy closure. Due to the nature of this trial, we do not anticipate the need to enroll more than 25 subjects in order to have a maximum of 60 subjects complete study follow up

#### **4.3. Study Outcomes**

##### **a. Primary Outcomes**

The primary outcomes for this trial are success or failure of exstrophy closure, urinary continence, operative time, length of hospital stay, and a record of all peri-operative and post-operative complications

##### **b. Secondary Outcomes**

The secondary outcome for this trial is improved identification of the pelvic floor anatomy during bladder exstrophy closure as reported subjectively by the surgeon at the time of surgery.

#### **4.4. Recruitment Information**

The PI will be responsible for approaching parents/guardians of potential participants. Potential participants will be identified and assessed for potential eligibility for study inclusion at the time of their routine Pediatric Urology clinic visits or inpatient consultations when their operative procedure is scheduled. Patients will be approached for possible inclusion in this study once the patient’s parents or legally authorized representative (LAR) have already decided to have the patient undergo the respective operative procedure.

#### **4.5. Informed Consent**

The PI and IRB approved study co-investigators will be responsible for conducting the informed consent discussions with the parents/LAR of potential participants. Discussions regarding study participation will take place in private areas after the patient and their parent/LAR have already decided to undergo the respective operative procedure. Enrollment in this research study will be presented as optional and purely voluntary. All risks of the study will be discussed. Parents or the legally authorized representative will be provided with the IRB approved consent form at their clinic visit or initial consultation. Patients or the LAR will be given as much time as needed to consider study participation. As many visits as necessary will be provided. The informed consent will be collected from those wishing to participate at a clinic visit or consultation prior to surgery or on the morning of the operative procedure

Competency to comprehend informed consent both for the research study will be assessed by the investigator. Only parents/legally authorized representatives of patients that are able to understand the consent form and comprehend the nature of the procedure will be enrolled.

## 5. Study Treatment

Study patients will be recruited from those patients of the PI and IRB approved co-investigators who require bladder exstrophy closure as part of routine medical care.

Once patients have agreed to participate in standard bladder exstrophy closure surgery, patients will be approached with regard to interest in participation in the clinical study as per Section 4.5 above. Study patient will undergo a pre-operative non-contrast T1 and T2 weighted pelvic MRI (routinely obtained with standard clinical care) in order to plan pelvic osteotomies (also as per the standard of care).

### **Description of the specific medical/surgical procedures involved in the use of the investigational Device(s)**

On the day of scheduled surgery, the patient will undergo routine pelvic osteotomies, pelvic floor dissection, bladder closure, and abdominal wall closure as per the standard of care.

Some images from the preoperative MRI will be loaded onto a software program by certified/trained members of the IRB approved study team. These images will then be used to identify and highlight the exact location of the levator muscle fibers, rectum, urethra, bladder, and pelvic bones when mobilizing the bladder and prostatic plates as well as during pelvic floor dissection.

During the osteotomy, standard external fixation pins (orthopedic metal pins that are placed in the pelvic bones and protrude through the patient's skin) are placed by orthopedic surgeons as is per standard of care prior to the pelvic floor dissection. After placement of the external fixation pins, a sterile reference array will be attached to the external fixation pins by means of a VectorVision® 2-pin fixator. These 2-pin fixators are specifically designed to accommodate orthopaedic fixator pins that are routinely used in multiple orthopaedic procedures including pelvic osteotomies. The reference array communicates with the VectorVision® work station (placed in the operating room away from the patient table) by means of infrared light.

The VectorVision® software will be used to access the patient's preoperative MRI images. Four anatomical landmarks (i.e. pubic tubercles, anterior superior iliac spines, etc.) are used to register the patient's anatomy. These landmarks can be identified on MRI and visually by the surgeon in the operative field. This is accomplished by taking a sterile probe or instrument that is connected to the VectorVision® image guided system stylus and placing it directly on or near the landmarks on the patient. These landmarks are registered to the IGS work station. The virtual image or spaces of interest (i.e. pelvic floor and bladder) are now correlated to the surgical environment by collecting the 3D position of the pre-determined anatomic landmarks with a tracked pointer probe and relating them with the corresponding features extracted from the pre-operative MRI image sets.

The stereotactic imaging (which can be viewed in 3 dimensions) will be displayed on a monitor in the operating room in real time. The VectorVision® system has several sterile instruments and probes that can be used to visualize where the instrument is in real-time. This capability will allow for stereotactic imaging, confirmation that the anatomical structures of interest have been identified by both the surgeon's eyes in the operative field and the radiologist's eyes on the image monitor and thus allow for placement of the instruments during dissection of the pelvic floor.

Once the pelvic floor has been properly identified with stereotactic confirmation, the VectorVision® device will no longer be used. The reference array will be removed from the external fixation pins on the patient, and surgery will continue as it routinely does during standard clinical practice.

Postoperatively, the patient will receive routine clinical postoperative care which includes placement in traction and the use of an external fixator to prevent separation of the pubic bones as per standard of care. A suprapubic tube as well as ureteral stents is also left in place. Prophylactic antibiotics are continued post-operatively to prevent renal scarring from vesicoureteric reflux that is usually present and the hospital stay will be three to four weeks. Prior to discharge from the hospital the suprapubic tube will be removed and the patient will be schedule to follow up at routine clinical visits that typically occur at 2 weeks, 1 month, 3 months, 6 months, and 12 months after discharge from the hospital.

Outcomes, including success or failure of exstrophy closure, urinary continence, operative time, length of hospital stay, and a record of all peri-operative and post-operative complications, will be collected quarterly from the patient's medical record from all follow up visits for the 12 months following the surgical procedure.

No change in participant's care will occur if the study ends or the participant withdraws.

## **6. Inclusion/Exclusion Criteria**

### **6.1 Inclusion Criteria:**

- a. Age 0-7 years
- b. Diagnosis of classic bladder exstrophy
- c. Scheduled to undergo bladder exstrophy closure by the principal investigator at Johns Hopkins Hospital's Broadway campus.
- d. All eligible participants will be children whose parents or legally authorized representatives have already agreed and are being scheduled for osteotomy and bladder exstrophy closure as determined by their pediatric urologist.
- e. Parent or legally authorized representative who is, in the opinion of the investigator, reliable and willing to make themselves and patient available for the duration of the study.
- f. Parent or legally authorized representative is able to complete and sign the informed consent document.
- g. Patient judged by the investigator to have bladders of sufficient size and elasticity to be suitable for immediate closure as evidenced by the PI's assessment of the patient's bladder template [16].
- h. Patient with cardiopulmonary function sufficient to tolerate general anesthesia as evidenced by the pediatrician's and anesthesiologists assessment of the patient's overall cardio-pulmonary status.
- i. Patients requiring ferromagnetic metal objects such as a metal pace maker during the OR procedure.

## 6.2 Exclusion Criteria

- a. Lack or withdrawal of consent for primary operative procedure.
- b. Parent or legally authorized representative who is, in the opinion of the investigator, not reliable or unwilling to make themselves and patient available for the duration of the study.
- c. Parent or legally authorized representative who is unable to understand, complete and/or sign the informed consent document. Non-English speaking parents will automatically be excluded if they are unable to read and understand the consent form.
- d. Patient who will not undergo osteotomy prior to closure for any reason

## 7. Investigational Devices

### 7.1 Cranial Image Guided Surgery System

#### a. Common Classification

Name BrainLAB Cranial Image Guided Surgery System

#### b. Trade Names

VectorVision Cranial  
VectorVision ENT  
Kolibri cranial  
Kolibri ENT  
Cranial Essential  
Cranial Unlimited  
ENT Essential  
ENT Unlimited

c. Regulatory Class: Instrument/Stereotaxic; Regulatory Class II

d. Manufacturer: BrainLAB, AG

### 7.2 iPlan Cranial Software

#### a. Common/Classification

Name Planning System

b. Trade Names iPlan Cranial; iPlan Stereotaxy; iPlan ENT; iPlan Spine; iPlan View

c. Regulatory Class: Stereotactic Instrument; Regulatory Class II

d. Manufacturer: BrainLAB, AG

### 7.3 VectorVision® 2-pin Fixator

a. Manufacturer: BrainLAB, AG

## 8. Study Statistics

### 8.1 Primary Outcome Variables

Primary outcome variables include the amount of time added to the operative time, the closure complication (fistula, dehiscence, prolapsed) rate, the post-operative complication rate, the need for repeat surgeries, and the length of hospital stay.

## **8.2 Secondary Outcome Variables**

The secondary outcome for this trial is improved identification of the pelvic floor anatomy during bladder exstrophy closure as reported subjectively by the surgeon at the time of surgery.

## **8.3 Statistical Plan and Sample Size**

The sample size was determined based on the average number of patients with bladder exstrophy who undergo closure during a calendar year at JHMI. It is estimated that 60 would be an adequate sample size. The results of this pilot study will be informally compared to previously published rates of the variables listed above for bladder exstrophy closure without the use of stereotactic imaging assistance.

Descriptive statistical analysis will be performed for all collected variables with counts, percents, median and interquartile range as appropriate. No formal statistical tests will be performed.

## **8.4 Early Stopping Rules**

No early stopping rules will be employed in this study.

# **9. Risks**

## **9.1. Risks Related to Standard Operative Procedure**

### **Surgery:**

The participant has already agreed to undergo an operation to help correct a pediatric urology issue. The risk and discomforts of the operation have already been explained and are covered under the informed consent that was signed for that particular procedure.

### **General Anesthesia:**

General anesthesia will be used during the primary operative procedure. All of the known risks associated with anesthesia apply including respiratory problems, stroke, low blood pressure, and death. Problems such as these are extremely rare in children. All anesthetic care will be directed by a certified pediatric anesthesiologist.

## **9.2. Risks Specific to Research Activities**

Soft tissue distortion that occurs during surgery or inaccuracies during registration of the virtual diagnostic images described in section 6.5 may cause the virtual image to misrepresent the patient's actual anatomy. However, this poses minimal risk to the patient as the image guidance will only be used as a supplement to direct visual inspection of patient's anatomy by the surgeon and will not be used as the primary source for visual guidance into the operating field.

Another risk is the possibility that the external fixator pins described in section 6.5 may shift from their original placement while applying the VectorVision® 2-pin fixator. Though this risk is unlikely, if this were to happen corrective measures would be taken to restore the

external fixator pins back to their appropriate position prior to continuation of the procedure.

Just as with use of any computerized equipment, there is a risk of equipment malfunction that may result in an increase in operating time. Overall, known risks are rare, but these and any unanticipated problems will be medically managed as appropriate, and reported to the IRB and FDA promptly as per DSMP.

### **9.3. Legal Risk**

There is a risk to confidentiality. Most participant related data will be stored in our institutions electronic medical record. This system requires authorized access and is password protected. Every effort will be made to keep the subjects' non-electronic records and consent forms safe by storing in a locked office. If members from the IRB or other Federal agency need to inspect records, they will be released. Hence, absolute confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications; however, subjects' identity will not be disclosed.

### **9.4. Financial Risk**

No additional costs to the patient are associated with the addition of VectorVision stereotactic imaging. The costs of the disposable instrumentation associated with VectorVision will be funded by the Department of Pediatric Urology.

### **9.5. Steps Taken to Minimize Risk**

Risks will be minimized through precautions set forth through standard operating room protocols, such as proper attire and scrub and monitored anesthesia. Hands will be washed before performing any invasive procedure. Personnel will follow "Universal/Standard Precautions" to prevent and minimize exposure to blood and body fluids. Personnel will wear standard operating room attire, which shall consist of a clean scrub suit, disposable surgical mask and cap. A surgical mask that fully covers the mouth and nose will be worn when entering the operating room (if sterile instruments are exposed or the operation is about to begin or is underway).

Every effort will be made to maintain participant confidentiality throughout the trial. Measures to help ensure protection include use of password-protected Excel spreadsheets for all study data. Patient study records will be kept in a locked office accessible to IRB approved study staff.

MRI registration errors and the possibility of soft tissue distortion that may occur to soft tissue as the result of the surgical procedure can lead to inaccuracies with the imaging system. Extra care will be taken to verify that anatomical structures that can be seen with the surgeon's eyes match up to the equivalent landmarks seen on the VectorVision system's virtual image to minimize risk of surgical error.

## **10. Benefits**

This study may benefit participants through more precise surgical dissection, yielding better outcomes and reduced complications

Classic bladder exstrophy is one of the largest birth defects affecting 1 out of 30,000 children that is correctable with surgery. Classic bladder exstrophy is where the bladder of a child, as well as the

abdominal wall and genitalia are not formed properly. Johns Hopkins is the leading center in the world for correction and research on this birth defect. Developing methods for other surgeons at centers with less experience to better understand and identify the anatomy involved with this surgery may help improve the success of the surgery worldwide.

## 11. Data and Safety Monitoring Plan

The research involves some risks to the participants. A group of designated faculty, that includes Pediatric Orthopedic Surgeon Dr. Michael Ain, Pediatric Anesthesiologist Dr. Sabine Kost-Byerly, and Adult Urologist Dr. Herbert Ballentine Carter, will be involved in safety monitoring. These individuals will be notified promptly for any serious adverse events or deaths and will perform routine monitoring and oversight reviews of the research and postoperative outcomes to assess for trends or risks that were not previously identified. In the event of an adverse event, unanticipated problem, or a study deviation the IRB will be notified within 24-48 hours and the research will be halted pending review. Per the Johns Hopkins IRB policy 103.6b, "Unanticipated problems involving risks to participants or others" is defined as: The information is unexpected in terms of nature, severity, or frequency, given:

- a. The research procedures described in the protocol and informed consent document; and
- b. The characteristics of the subject population being studied; and
- c. The information indicates that participants or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Also as per policy, the prompt reporting of unanticipated problems or events will occur as soon as possible after the PI learns of the event, but in all cases within 10 working days with the exception of death of a participant which must be reported within 3 working days.

Additionally, a team of designated faculty, including the PI's clinical fellow, the orthopedic surgeon (Paul Sponseller), and the radiologist (Aylin Tekes), will be present to monitor the patient during surgery. Standard safety monitoring by the anesthesiology team during surgery and post-operative nursing staff will monitor the patient for any safety concerns related to the surgery or immediate post-operative care.

### 11.1 Adverse Events

An adverse event (AE) is defined as an unusual and undesirable symptom or sign that occurs in participants during the clinical study. Adverse events include those clinically significant laboratory values and test results, concomitant illness, accident, medical occurrence or worsening of existing medical condition that emerge during study participation.

### 11.2 Adverse Event Grading

The investigator will evaluate the severity of each adverse event using the following definitions:

- *Mild* - event may be noticeable to subject; does not influence daily activities; usually does not require intervention.
- *Moderate* - event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

- *Severe* - event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed.

All participants will receive pre-op, operative, and post-operative care according to the standard of care at Johns Hopkins. Given the broad array of postoperative adverse events associated with an extensive surgery of this nature, AEs graded as ‘severe’ which are possibly, probably, or definitely attributable to the use of the investigational device will be recorded and monitored until the event has resolved to meet the definition of ‘mild’. All participants will receive care for all adverse events according to good clinical practice as per the standard of care at Johns Hopkins.

### **11.3 Serious Adverse Events (SAE)**

A serious adverse event will be defined as any adverse event that:

- Results in death
- Is immediately life-threatening – an adverse event which places the subject/patient at immediate risk of death from the adverse event as it occurred
- Results in permanent or substantial disability
- Results in or prolongs an existing in-patient hospitalization

### **11.4 Attribution of Adverse Events**

All adverse events will be further evaluated for attribution as per the following:

- Unrelated: Adverse event is clearly not related to the investigational agent.
- Unlikely: Adverse event is doubtfully related to the investigational agent.
- Possibly: Adverse event is possibly related to the investigational agent.
- Probably: Adverse event is probably related to the investigational agent.
- Definitely: Adverse event is definitely related to the investigational agent.

### **11.5 Plan for data collection and AE reporting**

Study outcomes, including success or failure of exstrophy closure, urinary continence, operative time, length of hospital stay, and a record of all peri-operative and post-operative complications, will be collected quarterly by IRB approved study staff from the patient’s medical record for 12 months post procedure.

Operative complications will be defined as complications that may be a direct effect of the quality of the operative procedure. Failure of exstrophy closure is defined as either a post-operative dehiscence, bladder prolapsed, or a vesicocutaneous fistula. These outcomes will be compared to previously established rates of success, complications, continence, etc.

Only those AE’s deemed as possibly, probably or definitely attributable to use of the investigational device will be collected and reported at the time of the annual IRB continuing renewal.

If a serious adverse event (SAE) occurs, the study investigator will complete and submit the Unanticipated Problem form or Problem/Event reporting mechanism via the eIRB. The investigator will also compile with urgent priority other relevant documentation (e.g., copies of test results,

hospital discharge summary, autopsy report, etc.). The IRB will be informed of all required SAE's within ten (10) days as per JHM IRB and institutional guidelines.

Serious adverse events will be reported to the FDA at the discretion of the principal investigator via the FDA Med Watch 3500 voluntary reporting mechanism.

**a. Death of study participant**

As per JHM IRB policy 103.6bi, "*Organization Policy on Reporting Death of a JHM Research Participant*," if a study participant dies within 30 days from the date of the investigational stereotactic bladder exstrophy closure surgery, whether expected or unexpected, the PI will report the death to the IRB and FDA promptly. Death not related to a risk of participation that was listed in the protocol or consent document and was more likely than not caused by the research procedures/study intervention will be reported to the IRB and to the FDA no later than 3 working days of when the PI receives the report of death. Deaths considered 'expected' due to the nature of the participant's underlying disease or condition or identified as caused by a possible risk of the intervention as described in the protocol and informed consent will be reported to the IRB no later than 10 working days of when the PI receives the report of death.

Additionally, if the PI receives information of the death of a JHM former participant who did not complete the protocol for whatever reason (including voluntary withdrawal or removal by the PI) the PI will report to the IRB the former participant's death as part of the next Continuing Review application for IRB review.

## **11.6 Plan for Data Management**

The PI will review study data on a quarterly basis and ensure that study documents are monitored every six months for the duration of the study for data accuracy and completeness. The PI will maintain a file of human subjects' research project documents including (at a minimum) the following items:

- a. A copy of the original human subjects research application submitted to the JHM-IRB
- b. A copy of the JHM IRB approved consent form.
- c. The original of each consent form signed by each participant enrolled in the research.
- d. A copy of all correspondence with the IRB, FDA, and others as appropriate
- e. A copy of all data derived from the study (case report forms, computer data, adverse event reports, drug/device accountability records etc.)

## **12. Data Handling and Record Keeping**

Per John Hopkins IRB record retention guideline (Nov. 2008) for investigational device research, the PI will assure that all essential study documents will be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

## References:

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